REMARKS

Claims 19-39 were previously pending in this application. Claims 19-39 are still pending for examination with claim 19 being an independent claim. No claims have been amended, canceled or added. No new matter has been added.

Objection to Information Disclosure Statement (IDS)

The Examiner has indicated that some of the references cited on the December 23, 2003 IDS have not been considered because prior application 08/738652 was not available to the Examiner. The Examiner requests that Applicants submit copies of the references cited in that IDS which were not initialed by the Examiner.

Applicants have met their burden for compliance with 37 CFR 1.98(a)(2). In order to advance prosecution Applicants will submit the requested references and a new form 1449. Applicants respectfully request that the Examiner consider each of the references and return an initialed copy of the 1449 to Applicants.

Double Patenting Rejection

Claims 19-39 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-19 of U.S. Patent No. 6,239,116.

Claims 19-39 were not obvious at the time of the invention over claims 1-19 of U.S. Patent No. 6,239,116 because claims 1-19 of U.S. Patent No. 6,239,116 do not suggest that the CpG oligonucleotide be administered to a subject having asthma. Claims 19-39 of the instant patent application include the limitation that the CpG oligonucleotide is administered to a subject to treat asthma.

Provisional Double Patenting Rejection

Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness type double patenting in view of claims 42-47, 49-53, 56, 57, 82-85, 90, 92, 94, 96, 98, 100, 102,

and 103 of co-pending U.S. Serial No. 09/337584. According to the Examiner, the claims are not patentably distinct from one another.

The rejection is a provisional one since none of the claims in the 09/337584 application have been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness type double patenting in view of claims 46, 52, 64, 71, 72, 74, and 80 of co-pending U.S. Serial No. 10/613739. According to the Examiner, the claims are not patentably distinct from one another.

The rejection is a provisional one since none of the claims in the 10/613739 application has been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness type double patenting in view of claims 22, 23, 31, 32, and 34-37 of co-pending U.S. Serial No. 10/769282. According to the Examiner, the claims are not patentably distinct from one another.

The rejection is a provisional one since none of the claims in the 10/769282 application has been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness type double patenting in view of claims 19-29 and 31-33 of co-pending U.S. Serial No. 10/894862. According to the Examiner, the claims are not patentably distinct from one another.

The rejection is a provisional one since none of the claims in the 10/894862 application has been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

Claims 19-39 are provisionally rejected under the judicially created doctrine of obviousness type double patenting in view of claims 42, 45-53, and 57-60 of co-pending U.S. Serial No. 09/337893. US 09/337893 was listed in the office action in one place as 09/337896, but it is applicants' belief that 09/337896 was a typographical error. Accordingly applicants have not

addressed a rejection in view of 09/337896. According to the Examiner, the claims are not patentably distinct from one another.

The rejection is a provisional one since none of the claims in the 09/337893 application has been found allowable. If any of the cited claims are found allowable, Applicants will consider filing a Terminal Disclaimer to overcome the rejection.

The examiner has requested that applicants identify other co-pending patent applications. In the subsequently filed IDS applicants will update the list of co-pending patent applications.

Rejection under 35 U.S.C. §112

Claims 19-39 have been rejected under 35 U.S.C. §112 first paragraph for a lack of enablement. The Examiner has indicated that a method for treating asthma using SEQ ID NO. 10 is enabled but that the use of other CpG containing oligonucleotides is not enabled. Applicants request reconsideration in light of this response.

Applicants have described a class of molecules (oligonucleotides) having a common structural motif (a CpG dinucleotide) that when administered to a subject results in an aspect of the immune response being altered, with a Th1 response being favored. This class of oligonucleotides is described throughout the specification and their ability to produce a Th1 favored immune response is not only described (e.g., see page 8, lines 22-23 and 25-27, page 9, lines 8-9 and page 53, line 26 – page 54, line 5) but data is presented *in vitro* and *in vivo* using an adequate number of different CpG containing oligonucleotides to meet the enablement requirement for the claimed invention.

The data in the application, including that represented in Tables 1-3, establishes that the unmethylated CpG is responsible for the immune stimulation. More than 40 oligonucleotides were tested. The data represented in Table 5 demonstrates that the immune stimulation has the characteristic pattern of a Th1 response. Eleven different oligonucleotides induced a Th1 cytokine profile, demonstrating the consistent stimulatory effect of CpG containing oligonucleotides.

It is believed that CpG containing oligonucleotides mimic bacterial DNA in their ability to promote an immune response. The inventors believed they discovered one of natures pathways

fundamental to the immune system. This discovery is described on page 35 of the specification under the heading "Teleological Basis of Immunostimulatory Nucleic Acids." It is taught that the stimulatory CpG motif, identified according to the invention, is common in microbial genomic DNA, but quite rare in vertebrate DNA. Experiments described in Example 3, in which methylation of bacterial DNA with CpG methylase was found to abolish mitogenicity, demonstrated that the difference in CpG status is the cause of immune stimulation by bacterial DNA. It is further taught that "Teleologically, it appears likely that lymphocyte activation by the CpG motif represents an immune defense mechanism that can thereby distinguish bacterial from host DNA."

The specification includes *in vitro* data on mouse and human cells, as well as *in vivo* data. Tables 1-3 demonstrate that many different CpG oligonucleotides are capable of activating murine B cells and inducing cytokine expression in murine cells *in vitro*. Table 5 depicts an experiment in which multiple CpG containing oligonucleotides were tested for their ability to induce cytokine expression in human cells. The experiment of Table 5 demonstrated that multiple CpG oligonucleotides were capable of inducing cytokine expression and notably an IL-12 response. Table 13 depicts the induction of IL-12 by human PBMC using a panel of CpG oligonucleotides. The data shown in Table 13 involved selecting data from two different subjects to demonstrate the extremes of the data (specification page 41 lines 5-8).

The data need not support that every CpG oligonucleotide work equivalently or even work at all. In Atlas Powder Co. v. E.I. du Pont de Nemours & Co., 750 F.2d 1569, 1576-77, 1984 (upholding district court decision that patent on emulsion formulations was valid even though it was, in the words of the defendant, a mere "list of candidate ingredients"), it was stated: "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. 'It is not a function of the claims to specifically exclude...possible inoperative substances,' In re Dinh-Nguyen, 492 F.2d 856, 858-59 (C.C.P.A. 1974)." That every CpG oligonucleotide would not work equivalently or that it is possible that some rare oligonucleotides might not work at all is not a sufficient basis for rejecting the claims.

The above-identified patent application is based on the discovery that a class of molecules that include a CpG motif promote a very specific and effective immune response. The asthmatic

immune response includes activation of the innate immune system (not antigen specific) and can also, but not necessarily, involve the adaptive immune response (antigen specific). As described in the specification, CpG oligonucleotides were shown to promote NK cell activation as well as to alter profiles of cytokines, independent of antigen administration. The specification describes the use of CpG alone for therapeutic purposes based on this discovery.

The methods for treating asthma are described throughout the application in terms of the administration of CpG as a therapeutic. It is taught that an immune profile which is consistent with the promotion of a Th1 favored response is important in asthma. The experimental work examining shifts in cytokine induction were achieved using CpG alone without an allergen. For instance, CpG oligonucleotides were used alone without antigen/allergen to produce Th1 biased cytokine induction in Table 5. No antigen was administered.

The immune system in an asthmatic person has cytokine activity that is imbalanced toward a Th2 response. One of ordinary skill in the art would have expected that CpG oligonucleotides would help restore a proper balance. CpG oligonucleotides alone would have been expected to act on the immune system to bias the cytokine profile away from a Th2 response.

Example 12 confirmed that a CpG containing oligonucleotide would have the ability to initiate *in vivo,* even in the presence of an antigen, a pattern of cytokine release which would drive the immune system toward a Th1 response and would treat asthma. Example 12 also confirmed that CpG not only shifts the cytokine response, but is effective in influencing important therapeutic aspects of asthma, such as infiltration of cells and fluid into the lungs. Based upon that teaching, those of ordinary skill in the art would have believed that CpG oligonucleotides would bias the immune system toward Th1, when given alone and even when given together with an antigen which otherwise would provoke a Th2 response.

The Examiner has cited several papers in support of the lack of enablement rejection and in particular in support of the argument that the state of the art at the time of the invention was unpredictable.

McCluskie et al 1999 (Molecular Med. 1999, 5/5:287-300) and Krieg et al 2000 (Immunology Today 2000, 21/10:521-526) have been cited for the proposition that biological

responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism.

McCluskie et al is an article describing DNA vaccines against Hepatitis B virus. On page 296, the page identified by the examiner, the reference mentions that one of the factors involved in influencing the Th bias of the response to DNA vaccines is the presence of CpG motifs. The reference is not relevant to the enablement of the pending claims because the pending claims do not encompass plasmid vectors (or DNA vaccines). The pending independent claims are directed to the use of oligonucleotides. The issues of predictability and therapeutic effectivity are very different for CpG oligonucleotides and DNA vaccines.

Krieg et al is a review article describing the uses of CpG oligonucleotides. The office action specifically points to page 524 of the reference in support of the examiner's argument that biological responses to the administration of CpG containing oligonucleotides vary depending on the mode of administration and the organism. Applicants do not see this teaching in the reference. In fact the reference teaches on page 524 that "Unlike many vaccine adjuvants that have been extremely effective in mice but disappointing in humans, CpG DNA is also highly effective in higher primates." This teaching does not support the examiner's assertion that the administration of CpG oligonucleotides varies depending on the organism. Furthermore, Krieg et al describe the usefulness of CpG oligonucleotides in producing a Th1 biased immune response. Page 524 of Krieg et al includes the following teaching:

> "These and subsequent studies have shown CpG DNA to be a more effective Th1-like adjuvant than complete Freund's, and to be effective with multiple types of antigens and routes of immunization including mucosal immunization (reviewed in Ref. 50). In fact, in a comparison of 19 different adjuvants, CpG DNA was found to be the strongest for inducing Th1-like immune response to tumor antigens[51]" and
> "The potent Th1 adjuvant effect of CpG can even override preexisting Th2 immune responses [5, 47]; it has been used as an adjuvant for allergy vaccines, where it induces Th1 responses to antigens in the presence of a preexisting Th2 response, leading to decreased symptoms following subsequent allergen inhalation ..... It should be stressed that CpG DNA is effective in asthma immunotherapy even when given as a stand-alone agent without allergen." [Emphasis added]

The Examiner has cited Wohleben et al (TRENDS in Immunology, 2001 22/11:618-626) in support of 2 arguments: 1) that the "state of the art questions whether 'CpG-ODNs can be used in humans to inhibit the development of asthma?'" and 2) that Wohleben teaches that "all approaches that induce Th1 responses have the potential side-effects of Th1cell-mediated inflammation potentially causing serious tissue damage." The applicants respectfully disagree with the Examiner's characterization of the reference.

Wohleben et al actually provides a favorable view of CpG oligonucleotides and their usefulness in the treatment of asthma. The use of CpG oligonucleotides is identified in the abstract and conclusion of the paper as one of "the most promising approaches" for the treatment of atopic disease and particularly asthma. Even the cited paragraph on page 620 relates to the expectation that CpG oligonucleotides will be effective in humans. It is taught that the "results obtained from animal models suggest that it is probable that these approaches might also be successful in humans to reduce the development of atopic disorders." (Page 620 second column first paragraph, emphasis added) and "This suggests that the treatment of humans with CpG-ODNs could be very effective in inhibiting the development of asthma." (Page 620 second column first paragraph). Thus, the teachings found in Wohleben et al are not sufficient evidence that the invention was not enabled at the time of filing of the patent application.

Further, the teachings of Wohleben et al with respect to potential side effects do not support a lack of enablement of the claims. Wohleben et al teach on page 620 immediately following the discussion of side effects that "it is totally unclear if this can also occur in healthy rodents or, more importantly, humans." (Page 620 second column first paragraph). Additionally the issue of whether a drug is safe and has no side effects is not an appropriate test for enablement. MPEP2164.01(c). "The applicant need not demonstrate that the invention is completely safe." In fact, one cannot possibly determine the parameters of safety without a controlled clinical trial, and it is well established that a clinical trial is not required for enablement.

Furthermore, the Wohleben et al reference, as well as the others cited for safety concerns and discussed in more detail below, do not suggest that use of CpG would be unsafe. All drugs have some side effects. The references at best suggest that care should be taken to see if there may

be certain patients for which the compound might be contraindicated. This is the type of inquiry made by those of ordinary skill in the art respecting all drugs. There is no evidence in any of the cited papers that CpG oligonucleotides would be unsuitable for the treatment of asthma. To the contrary, the cited papers, published years after the filing date, continue to support the view that CpG oligonucleotides should be advanced through clinical trials for the treatment of asthma. One of ordinary skill in the art would have believed, based on the data in the application, that CpG oligonucleotides would be well suited as clinical trial candidates for the treatment of asthma. The papers cited for safety issues have not altered that view.

The Examiner has cited the Kline et al 2002 (Am. J. Physiol. Lung Cell Mol. Physiol., 2002, 283:L170-L179) and Kline et al 1998 (J Immunol 1998, 160: 2555-2559) references to demonstrate that the use of CpG alone in some instances is not effective for the treatment of asthma. The Examiner asserts that Kline 2002 teaches that a single treatment of CpG-ODN alone was ineffective in reducing the manifestations consistent with asthma in this animal model. The section of the paper identified by the Examiner on page L172 relates to an experiment designed to model "persistent asthma in humans, who, by current standards of treatment, require intensive anti-inflammatory therapy." The claimed invention does not require that persistent asthma be treated with a single dose of CpG. Doses are within the purview of those skilled in the art, and the data in the paper supports that monotherapy at appropriate doses can work. In fact, many drugs including other drugs for treating chronic asthma are not effective as a single dose.

The Examiner has also indicated that Kline 2002 teaches that "splenocytes from OVA-treated mice did not develop an antigen specific Th1 phenotype. However mice treated with CpG ODN and OVA had a marked shift toward a Th1 response to antigen as well as reduction in airway eosinophilia, serum IgE and bronchial hyperreactivity (p. L176, col. 2)." (Office Action page 10). This statement does not support a lack of enablement of the claimed invention. The lack of development of a Th1 phenotype in mice in response to OVA treatment is not inconsistent with the invention. The second sentence is consistent with the utility of the invention.

Weiner (J. Leukocyte Biology, 2000, 68:456-463) is cited for the proposition that the molecular mechanism of CpG is unknown. Knowledge of the mechanism of action isn't necessary,

particularly in view of the detailed knowledge at the time the patent application was filed of the cellular effects of CpG oligonucleotides. The patent application identifies consistent changes in the immune system at the cellular level that occur in response to CpG administration and which are therapeutically relevant. Additionally, Table 1 of Weiner lists examples of cellular effects arising from immunostimulatory CpG ODN. A lack of understanding of the molecular mechanism does not render the cellular results unpredictable. Other statements in Weiner are consistent with enablement of the claimed invention. For instance it is taught on page 456 1st column second full paragraph that "Studies to date suggest CpG DNA could have significant therapeutic promise in the treatment of a variety of disorders, including infectious disease, allergy, and cancer." Page 457 under "In vivo effects of CpG ODN" teaches that "extensive studies have been done in rodents, and some studies have been done in non-human primates. The observed *in vivo* data fits well with the *in vitro* data outlined above."

Agrawal et al (Molecular Med. Today 2000, 6:72-81) has been cited in support of the assertion that the incorporation and positioning of chemical modifications relative to the CpG dinucleotide are highly unpredictable. In particular, the examiner has identified pages 78-80 as being particularly relevant. Agrawal et al is a review article describing antisense oligonucleotides. The authors suggest on page 78 that in order to *reduce* non-antisense related activity it is best to avoid CpG motifs. The authors also indicate that if it is not possible to avoid CpG motifs, then it is possible to make one of 3 modifications to reduce the CpG activity of the oligonucleotide. One of the suggested modifications is to replace the cytosine base of the CpG with a 5-methyl cytosine base. The instant specification teaches that a CpG containing oligonucleotide has an unmethylated C in the CpG motif. Further, the cited section of Agrawal et al teaches that the proposed 3 modifications "significantly reduced side effects". Agrawal et al does not teach that immune stimulation was abolished with any of these proposed modifications, just reduced.

Satoh et al. (Fukushima Igaku Zasshi 2002, 52/3:237-250) was cited in order to demonstrate that CpG was associated with dangerous side effects. The Satoh et al. reference is an abstract describing a study on the effects of CpG oligonucleotides administered subcutaneously to mice that are treated with DNFB. It was concluded that CpG oligonucleotides were responsible for worsening

of the allergic contact dermatitis (ACD) induced by DNFB. As mentioned above with respect to Wohleben et al the issue of whether a drug is safe and has no side effects is not an appropriate test for enablement. Additionally, the teachings of the Satoh et al reference are not sufficient to establish a lack of enablement for the claimed invention. The ACD is caused by DNFB treatment. The fact that CpG oligonucleotides may contribute to type IV hypersensitivity responses initiated by DNFB does not establish that CpG oligonucleotides would cause ACD in the absence of DNFB.

The Examiner has cited Dziadzio et al (Handbook of Experimental Pharmacology 2004, 161:273-285) as teaching that DNA vaccination for allergic disease requires further evaluation. However, Dziadzio et al actually teaches that CpG containing oligonucleotides are encouraging as potential therapies for allergic disease. After summarizing several sets of data on page 280, Dziadzio et al teach:

> "These data suggest that ISS-ODN can induce a Th1 phenotype prior to allergen exposure. It appears that even without the presence of allergen, CpG motifs can induce a Th1 phenotype in multiple cell types including B cells, antigen-presenting cells (macrophages, dendritic cells), T cells, and NK cells. The expression of Th1 cytokines along with an upregulation of costimulatory molecules on these cells underscores the importance of ISS-ODN in Th1 and innate immune responses. The persistence of a Th1 response after antigen challenge in sensitized mice is encouraging as potential therapy for allergic disease." (page 280, 2nd-3rd full paragraphs).

The teachings of Dziadzio et al as a whole do not support a finding that the claimed invention was unpredictable at the time of filing of the patent application.

A review article by Barnes (European J. Internal Medicine, 2000, 11:9-20) was also cited by the Examiner. Applicants were also directed to see Hussain et al J. Invest. Dermatol. Symp. Proc. 2004, 9:23-28 and Serebrisky et al J. Immunology, 2000, 165:5906-5912 without further comment. Barnes was cited for the teaching that "immunostimulatory oligonucleotides are potent inducers of Th1 cytokines and in mice, administration of CpG-ODN increases the ratio of Th1 to Th2 cells, decreases formation of specific IgE and reduces the eosinophilic response of allergen".... and..."that the animal studies encourage the possibility that vaccination might prevent or cure atopic disease in the future." These statements from Barnes do not support the unpredictability of

the invention. If anything these statements are consistent with and supportive of the utility of the invention.

The Examiner has cited Van Uden et al (J. Allergy Clin. Immunol., 1999, 104:902-910) for the concept that each ISS has a minimum length limitation and that potential side effects associated with treatment must be considered. With respect to the section of the paper that refers to the length of ODN, the authors do not conclude that there is a specific rule for the length of the ODN. The authors hypothesize that different lengths and flanking sequences have an impact on the activity of the ODN. The patent application as filed confirms that certain motifs and lengths are preferred. However, it is believed that most unmethylated CpG containing oligonucleotide within the scope of the claims would have the ability to initiate *in vivo* a pattern of cytokine release which would drive the immune system toward a Th1 response when administered in an appropriate dosage.

The examiner quotes some language from page 907 column 2 and page 908 column 1 related to the issue of side effects associated with CpG oligonucleotide administration. Each of these statements, however, is taken out of context. After the quoted section the authors point out that such side effects have not been observed. For example, the Examiner has pointed to the statement on page 907 that "There is always the possibility of unwanted effects of the powerful immune stimulation that ISS delivers" and compared the effects of CpG with LPS (Office Action page 12). In contrast to the implications from the language quoted in the office action, immediately following that paragraph the authors conclude

> "Although these reports demonstrate the possibility of shock in extreme cases of sensitization or concurrent LPS exposure, there has never been a reported case of ISS alone causing shock in any kind of healthy animal at any dose." (Page 908 column 1 lines 2-6) and
> "We and others have never observed gross inflammation in response to ISS in ODN or plasmid form in any experimental animals or humans." (page 908 first column first full paragraph)

The Examiner has also stated that Van Uden et al teaches that "ISS could cause excessive local inflammation as seen with other powerful Th1 adjuvants, such as CFA." In contrast to this

statement the authors point out an experiment in which bacterial DNA complexed with CFA is injected into mice. It is concluded that

> "When the mixture is given to preautoimmune NZB/NZW F1 mice, they develop antibodies that cross-react with mammalian DNA, but surprisingly they are actually protected from their spontaneous autoimmune disease. There still are no examples of ISS directly causing any type of autoimmune disease in animal models." (page 908 paragraph bridging columns 1 and 2).

In addition to the discussion of safety issues raised with respect to the cited references, Applicants point out that Several Phase I and II studies have been performed in humans to date. For instance, subcutaneous administration, like that in the Satoh reference, has been performed in humans for a cancer trial. The data are described in Kim et al., Blood, volume 4, issue 11, abstract # 743, Nov. 16, 2004 (copy enclosed). Toxic effects that would halt further human trials were not observed, even though the patients were provided CpG oligonucleotides in very aggressive doses. The abstract concludes that "weekly doses up to 0.36 mg/kg have been well tolerated." The results of this clinical trial are submitted herein to demonstrate that CpG oligonucleotides have been safely administered to humans, and not to demonstrate efficacy of the compounds. This clinical trial demonstrates that CpG oligonucleotides have been administered to humans and were well tolerated.

As described above, numerous working examples were provided in the specification. These examples in combination with the description in the specification were sufficient to enable one of skill in the art to practice the invention over the full scope of the claims. Consistent with the descriptions, a number of studies published since the filing of the patent application have reiterated, as set forth in the specification, that CpG oligonucleotides having different structures but maintaining the critical CpG motif result in an altered immune response. For instance, US Patent Application Serial No. 10/644,052 published as US Publication No 2005/0059619 A1 describes numerous examples of CpG oligonucleotides that stimulate an immune response.

Thus, one of ordinary skill in the art, based on the teachings in the patent application, would have reasonably expected the claimed invention to work over the full scope of the claims.

Rejection under 35 U.S.C. §112

Claims 19-39 have been rejected under 35 U.S.C. §112 second paragraph as being indefinite because of omitted elements in the preamble. According to the rejection the preamble does not specify if the treatment is for a subject or is an in vitro treatment.

Claims 19-39 are definite. The preamble clearly states that the claimed method is a method for treating asthma. The body of the claim recites a step of administering an oligonucleotide to a subject to treat asthma. It is clear from the language of the claim that the claim covers an *in vivo* method rather than an *in vitro* method. It is respectfully requested that the rejection be withdrawn.

CONCLUSION

If the Examiner believes, after this Response, that the application is not in condition for allowance, the Examiner is requested to call the Applicant's attorney at the telephone number listed below. If this response is not considered timely filed and if a request for an extension of time is otherwise absent, Applicant hereby requests any necessary extension of time. If there is a fee occasioned by this response, including an extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825. No new matter has been added.

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Respectfully submitted,

By _____

Helen C. Lockhart
Registration No.: 39,248
WOLF, GREENFIELD & SACKS, P.C.
Federal Reserve Plaza
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
(617) 646-8000